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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/677,574

10/03/2000

Shuwei Yang

IVGN 195.1 CON

1982

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EXAMINER

HUTSON, RICHARD G

ART UNIT

PAPER NUMBER

1652

MAIL DATE

DELIVERY MODE

11/28/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/677,574

Applicant(s)

YANG ET AL.

Examiner

Richard G. Hutson

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8/17/2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,6-9,14,17,20,37-40,69 and 71-75 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,6-9,14,17,20,37-40,69 and 71-75 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants filing of an appeal brief on 8/17/2007 is acknowledged, however, upon further consideration, the finality of the previous office action has been removed and the following supplemental non-final office action deemed appropriate.

Claims 2, 6-9, 14, 17, 20, 37-40, 69 and 71-75 are present and at issue for examination.

Applicants' arguments filed on 8/17/2007, have been fully considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 6-9, 14, 17, 20, 37-40, 69 and 71-75 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action. In response to this rejection applicants have filed a brief arguing applicant's position.

In applicants submitted Brief, applicants continue to assert that the claims relate to *Thermatoga neapolitana* (Tne) DNA polymerases modified to reduce or eliminate

nucleotide misincorporation during nucleic acid synthesis and that the claimed DNA polymerases comprise substitutions at amino acids Arg722 and Lys726 (Arg722/Lys726 mutants) or at amino acids Arg722 and Phe730 (Arg722/Phe730 mutants). Applicants submit that the claimed Arg722/Lys726 mutants have an amino acid substitution at position Arg722 (i. e., with Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, or Val) and an amino acid substitution at position Lys726 (i.e., with Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Phe, Pro, Ser, Thr, Trp, Tyr, or Val) and that Likewise, the claimed Arg722/Phe730 mutants have an amino acid substitution at position Arg722 (i. e., with Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, or Val) and an amino acid substitution at position Phe730 (i.e., with Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Pro, Ser, Thr, Trp, Tyr, or Val).

Applicants position with respect to the Arg 722 and Lys726 double mutant is acknowledged and has always been accepted. This is not the situation for the Arg722 and Phe730 double mutant.

In applicants submitted Brief, applicants continue to assert that applicants specification clearly discloses the claimed Arg722/Phe730 mutant Tne DNA polymerases in that applicants specification discloses that, in addition to the substitutions described for reducing nucleotide misincorporation, mutant polymerases may contain other modifications. Applicants submit that the specification discloses that Tne DNA polymerases having Arg722 and Phe730 mutations. And the specification indicates that Arg722 of Tne may be substituted with any other amino acid including

Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, i Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val and the specification indicates that amino acid Phe730 may be substituted with any other amino acid including Ala, Arg, Asn, Asp, Cys Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Pro, Ser, Thr, Trp, Tyr, and Val. Applicants submit that furthermore, the Specification discloses at least six working example of such Arg722/F730 double mutants of the Tne DNA polymerase (including various Arg722 substitutions combined with F730A or F730Y substitutions). See Specification Example 14 on page 46 and Example 17 on page 17.

Applicant's complete argument is acknowledged and has been carefully considered, however, is not found persuasive on the basis that applicants pointed to support for the claimed genus of mutations are not supported by the recited species (i.e. any mutation of Phe730 in combination with the mutation Arg 722 is not supported by applicant's recited species of F730A and F730Y).

For the reasons previously stated and repeated herein the rejection based upon new matter is maintained.

Claims 2, 6-9, 14, 17, 20, 37-40, 69, 71-75 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is recognized that this is a similar rejection as that which was previously made over similar claims on 4/8/2005. Upon further consideration it has been decided that this rejection still applies to the claims as they currently exist.

Claims 2, 6-9, 14, 17, 20, 37-40, 69, 71-75 are directed to all possible Poll I type mutant *Tne* DNA polymerase comprising a modification that reduces or eliminates misincorporation of nucleotides comprising positions Arg 722 and Lys 726 or Arg 722 and Phe 730. The specification, however, only provides those representative species of mutant *Tne* DNA polymerases in which the mutations reduce or eliminate misincorporation of nucleotides consisting of the specific Arg722/ Lys 726 mutations or specific Arg722/Phe730 mutations, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species, sufficient to describe additional mutations that reduce or eliminate misincorporation of nucleotides. The specification also fails to describe additional representative species of these mutant polymerases by any identifying structural characteristics or properties other than the activities recited in claim 3, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 2, 6-9, 14, 17, 20, 37-40, 69, 71-75 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a Pol I type mutant Tne DNA polymerase wherein said Tne DNA polymerase consists of the specific amino acid modification of positions Arg 722 and Lys 726, does not reasonably provide enablement for any Pol I type mutant Tne DNA polymerase comprising a modification that reduces or eliminates misincorporation of nucleotides comprising positions Arg 722 and Lys 726 or Arg 722 and Phe 730. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 2, 6-9, 14, 17, 20, 37-40, 69, 71-75 are so broad as to encompass any Pol I type mutant Tne DNA polymerase comprising a modification that reduces or eliminates misincorporation of nucleotides comprising positions Arg 722 and Lys 726 or Arg 722 and Phe 730. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of

mutant polymerases broadly encompassed by the claims. The claims rejected under this section of U.S.C. 112, first paragraph, place minimal if any structural limits on the claimed enzymes. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that Pol I type mutant Tne DNA polymerase wherein said Tne DNA polymerase consists of the specific modification of positions Arg 722 and Lys 726 or Arg 722 and Phe 730.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any Pol I type mutant Tne DNA polymerase comprising a modification that reduces or eliminates misincorporation of

nucleotides comprising positions Arg 722 and Lys 726 or Arg 722 and Phe 730 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting polymerase, exonuclease and proofreading activity; (B) the general tolerance of Tne DNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a Tne DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the polymerase, exonuclease and proofreading activity desired and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those mutant DNA polymerases of the claimed genus having the reduced or eliminated misincorporation activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any Pol I type mutant Tne DNA polymerase comprising a modification that reduces or eliminates misincorporation of nucleotides comprising positions Arg 722 and Lys 726 or

Arg 722 and Phe 730. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those mutants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

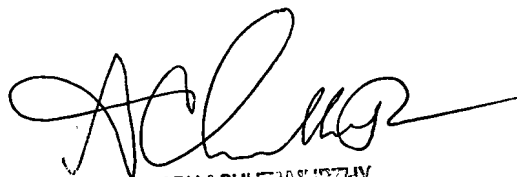
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11/26/2007



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